52. (new) The method according to claim 43, in which the disorder is selected from the group consisting of systemic inflammatory response syndrome, ischemia reperfusion, anaphylasis and allograft rejection.

## REMARKS

Claims 1-6 and 12-14 have been canceled. New claims 43-52 have been added to more distinctly claim that which Applicants regard as the invention. No new matter has been added.

3. **Priority Date**

It is stated that provisional applications 60/132,748 and 60/157,384 do not provide an adequate description of an antibody to the specific epitope of a prekallikrein-H-kininogen complex nor a human antibody.

In response, Applicants respectfully point out that claims 12-14 have been canceled. New claims 43-52 are directed to administering antibodies raised against heparin-binding protein in an amount effective to decrease release of bradykinin and attenuate the effect of heparin-binding protein on endothelial cell permeability. Both provisional applications do describe the generation of a human monoclonal and polyclonal antibodies to HBP (see page 19, lines 25-30 for polyclonal antibodies and page 20, lines 1-9 for monoclonal antibodies in application serial no. 60/132,748 and analogously, page 17, line 23 to page 18, line 3 in application serial no. 60/157,384 for monoclonal and polyclonal antibodies). General descriptions are also provided on page 7, lines 8-17 in application serial no. 60/132,748 and on page 6, lines 27-32 in application serial no. 60/157,384. Furthermore, it is stated in the first paragraph of the "SUMMARY OF THE INVENTION" in both applications:

> It has surprisingly been found that heparin-binding protein serves as a signaling link in neutrophil-induced vascular leakage and activation of the contact phase system with concomitant

formation of bradykinin and that it specifically plays a role in the PK mediated cleavage of HK to obtain the bradykinin sequence. Additionally, it has been found that antagonists of HBP decrease the permeability of endothelial cells.

Applicants further point out that the effect of anti-HBP antibodies on endothelial cell permeability and evidence of HBP interaction with kininogen is shown in Example 2 of both provisional applications (see, for example, page 24, lines 17-28 which contains the section "Inhibition of HBP-induced increase in EC permeability by peptide HKH20-treatment"). Therefore, Applicants should be entitled to the priority dates of the two provisional applications.

**2. The Information Disclosure Statement**

It is asserted that the Applicants is required to provide a full citation including a journal source and publication date for the Petersen et al. and Heinzelmann et al. references. In response, Applicants note that the Petersen and Heinzelmann references are Heinzelmann et al., 1998, Infection and Immunity 66:5842-5847 and Petersen et al., 1993, Eur. J. Biochem. 214:271-279. These are actually listed in the Information Disclosure Statement.

**3. Formal Drawings**

Corrected formal drawings will be submitted upon issuance of a Notice of Allowance.

4. **The Rejections Under 35 U.S.C. §112, Second Paragraph**

Claims 1-6 and 12-14 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is asserted that claims 1-6 and 12-14 are indefinite in that they only describe the compositions of interest by the arbitrary protein name "HBP".

In response, Applicants note that HBP is defined in the specification on page 11, lines 11-19. It is well-established case law that the words of a claim cannot be read in a vacuum but rather must be read in light of the specification and what is known in the art. *In re Moore*, 169 USPQ 236 (CCPA 1971). Thus, while the term "heparin-binding protein" read on its own may not be clear, when read in the context of the specification and the plain meaning of the word as it is understood by those skilled in the art, it is unquestionably definite as to what is intended.

However, in order to advance prosecution, claims 1-6 and 12-14 have been canceled. New claims 43-52 have been added. New claim 43 recites that heparin-binding protein (HBP) is (i) proteolytically inactive; (ii) stored in the azurophil granules of polymorphonuclear leukocytes and (iii) a chemoattractant for monocytes and/or activates monocytes.

In view of the cancellation of claims 1-6 and 12-14 and the addition of new claims 43-52, Applicants assert that the rejection under 35 U.S.C. §112, second paragraph has been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

**5. The Rejections Under 35 U.S.C. §112, First Paragraph**

Claims 12-14 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the Examiner's view, although the disclosure appears to support a role for HBP in the release of bradykinin from H-kininogen after cleavage by kallikrein, the disclosure does not appear to enable the actual binding of an epitope of HBP to the prekallikrein-H-kininogen complex, it does not appear to enable a monoclonal antibody to the proposed epitope of HBP. Furthermore, the Examiner states:

> However, although Applicant provides evidence that blocking HBP (by binding to aprotinin) or blocking various steps in the direct activation of bradykinin inhibits the HBP-induced

> increase in EC permeability; it is unpredictable as to whether HBP and the prekallikrein-H-kininogen complex directly interact (i.e., than epitope of HBP specifically binds the pekallikrein-H-kininogen complex), or whether intermediaries exist that mediate the observed effect. In the absence of objective evidence or working examples indicating that an epitope on HBP specifically binds the prekallikrein-H-kininogen complex; the skilled artisan would not reasonably predict that an antibody that specifically binds to an epitope of HBP, wherein said epitope binds the prekallikrein H-kininogen complex, could be used to[sic] as an HBP antagonist in the prevention or treatment of any disorder. Before the skilled artisan would have a reasonable expectation of successfully producing a monoclonal antibody to the epitope, the skilled artisan would first have to ascertain whether or not an HBP epitope that binds the prekallikrein-H-kininogen complex exists....

In response, Applicants respectfully point out that claims 12-14 have been canceled. New claims 43-52 have been added. As noted above, new claim 43 is directed to a method for preventing or treating a disorder resulting from release of bradykinin and alterations in endothelial cell permeability in a mammal, wherein said mammal produces heparin binding protein (HBP) that is (i) proteolytically inactive; (ii) stored in the azurophil granules of polymorphonuclear leukocytes and (iii) a chemoattractant for monocytes and/or activates monocytes, wherein said heparin binding protein interacts with kininogen resulting in release of bradykinin and said heparin-binding protein induces alterations in endothelial cell permeability in said mammal, said method comprising administering to said mammal in need thereof, an amount of an anti-heparin binding protein antibody in an amount effective to decrease release of bradykinin and in an amount effective to attenuate said alterations in endothelial cell permeability in said mammal. New claim 43 is supported by the specification on page 24, line 28 to page 25, line 17 (effect of anti-HBP antibodies on endothelial cell permeability) and on page 27, lines 16-29 (interaction of HBP with kininogen). Therefore, new claims 43-52 are enabled by the specification.

In view of the cancellation of claims 12-14 and the addition of new claims 43-52, Applicants assert that the rejection of prior claims 12-14 have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

## 6. The Rejection of Claims 1-6 and 12-14 Under 35 U.S.C. §112, First Paragraph

Claims 1-6 and claims 12-14 (if an epitope of HBP that binds the prekallikrein-H-kininogen complex is subsequently shown to be enabled) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for at least a method of reducing or inhibiting an inflammatory disorder mediated at least in part by bradykinin release, does not provide enablement for a method of preventing or treating systemic inflammatory response syndrome or other disorders which involve multiple mediators in addition to bradykinin. Specifically, it is stated:

> Although bradykinin is known to reproduce some of the characteristic associated with the inflammatory state, such as vasodilation and pain (citation omitted) the disorders recited by Applicant can involve many additional mediators. For example, systemic inflammatory response syndrome is itself a collection of conditions associated with inflammation. As reviewed by Grunfeld et al. (citation omitted), systemic inflammatory response syndrome encompasses such conditions as sepsis or even the response to multiple trauma (e.g., "Background of the Invention", especially 1st paragraph). Grunfield goes on to note that, at least with respect to the specific systemic inflammatory response syndrome condition of sepsis, many of the toxic effects are mediated by cytokines, hormones, and other small molecules (e.g., bridging paragraph columns 1 and 2). Further, Grunfield et al. conclude that treatment will need to combine a plurality of approaches in view of the large cascade of pro-inflammatory cytokines released (e.g., see especially column 2 at lines 4-13). Therefore, it is highly unpredictable that a single therapeutic modality, such as administering an antagonist of HBP, would be sufficient to treat systemic inflammatory response syndrome.

> In addition, although in some of the conditions encompassed by the term systemic inflammatory response syndrome, the timing of the insult/trigger is known (e.g., in surgery induced trauma), in other condition encompassed by this term the timing is not known (e.g., sepsis). The skilled artisan would expect that a method of preventing a disorder in which the timing of the insult/trigger is not known would be highly unpredictable. Therefore the skilled artisan would to reasonably expect that the invention could be used in preventative methods commensurate with the scope of the conditions recited in the instant claims.

Applicants respectfully traverse the rejection for a number of reasons. First, Applicants respectfully point out that the claims of Grunfield only require a single therapeutic modality, PTHrP antibodies. Furthermore, Grunfield in the specification states that the invention is directed to the use of PTHrP antagonists. The Examples in Grunfield et al. are directed to showing the effect of antiserum directed against PTHrP on LPS-induced lethality; no other therapeutic agent was used. It is pointed out in Grunfield that though PTHrP antagonists can be used with other therapeutic agents, the combination therapy is optional (see paragraph bridging columns 4 and 5). Furthermore, single modality treatments for sepsis are well known in the art. For example, it is noted in column 5, lines 20-30 that BPI can be used for the treatment of sepsis.

Secondly, Applicants wish to clarify that claim 43 is directed to using HBP to prevent or treat a disorder resulting from release of bradykinin and alterations in endothelial cell permeability in a mammal, by administering an amount of HBP effective to decrease release of bradykinin and in an amount effective to attenuate alterations in endothelial cell permeability in said mammal. Therefore, the method recited in claim 43 is directed to preventing or treating a disorder by decreasing the release of bradykinin in the mammal. Applicants have therefore clearly recited a specific means for preventing as well as treating a disorder resulting from the release of bradykinin in a mammal.

In view of the above arguments and remarks, Applicants assert that the rejections under 35 U.S.C. §112, first paragraph have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

## 7. The Rejections Under 35 U.S.C. §102

Claims 1 and 6 have been rejected under 35 U.S.C. §102(e) as anticipated by Oppenhelm et al. as evidenced by Rasmussen et al. Applicants traverse the rejection. However, in order to advance prosecution, Applicants have canceled claims 1-6. However, Applicants reserve the right to file subsequent continuation or divisional applications directed to the canceled subject matter.

In view of the cancellation of claims 1-6, Applicants respectfully request that the rejections be withdrawn.

## 8. The Rejections Under 35 U.S.C. §103

Claims 1-6 have been rejected under 35 U.S.C. §103 as being unpatentable over Oppenhelm et al. as evidenced by Rasmussen et al. in view of Grunfield et al. Applicants traverse the rejection. However, in order to advance prosecution, Applicants have canceled claims 1-6. However, Applicants reserve the right to file subsequent continuation or divisional applications directed to the canceled subject matter.

In view of the cancellation of claims 1-6, Applicants respectfully request that the rejections be withdrawn.

## 9. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited

to contact the undersigned by telephone at (914) 712-0093 if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: October 11, 2001

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